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=> s AAV (3a) (ITR or invert? terminal repeat)  
L1 178 AAV (3A) (ITR OR INVERT? TERMINAL REPEAT)

=> s l1 and hairpin  
L2 23 L1 AND HAIRPIN

=> dup rem l2  
PROCESSING COMPLETED FOR L2  
L3 11 DUP REM L2 (12 DUPLICATES REMOVED)

=> d bib abs 1-  
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L3 ANSWER 1 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN

AN 2004:292108 CAPLUS <<LOGINID::20060811>>

DN 140:315046

TI \*\*\*AAV\*\*\* \*\*\*ITR\*\*\* with a pair of \*\*\*hairpin\*\*\* loop as part  
of nucleic acid drug comprising biotin PNA-clamp and streptavidin for  
treating tumor

IN Wagner, Thomas E.; Yu, Xianzhang

PA Greenville Hospital System, USA

SO PCT Int. Appl., 23 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI WO 2004029278	A2	20040408	WO 2003-US29990	20030925
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WO 2004029278	A3	20040610		
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W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,  
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE,  
GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK,  
LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ,  
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CA 2500397 AA 20040408 CA 2003-2500397 20030925  
AU 2003278882 A1 20040419 AU 2003-278882 20030925  
US 2004137626 A1 20040715 US 2003-669641 20030925  
EP 1551859 A2 20050713 EP 2003-770397 20030925  
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,  
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK

PRAI US 2002-413450P P 20020926

WO 2003-US29990 W 20030925

AB The present invention relates to a stabilized nucleic acid that kills  
tumor cells and methods for producing the same. Specifically, the nucleic  
acid drug comprises pairs of \*\*\*AAV\*\*\* viral \*\*\*inverted\*\*\*  
\*\*\*terminal\*\*\* \*\*\*repeat\*\*\* \*\*\*hairpin\*\*\* loops which elicit  
cell apoptosis. The nucleic acid drug comprises nuclear localization  
signal peptide assocd. with said nucleic acid drug via a PNA-clamp,  
wherein said PNA-clamp comprises a biotin mol. that is bound to a  
streptavidin mol., wherein said streptavidin mol. comprises at least one  
nuclear localization signal peptide, and wherein said PNA-clamp anneals to  
a target sequence present in said nucleic acid drug. The invention  
provides the sequence of adeno-assocd. virus inverted terminal repeat.  
The present invention also provides methods for making such a stabilized  
nucleic acid drug as well as methods for targeting the drug to a cell  
nucleus or genome. Accordingly, the nucleic acid drug of the present  
invention is useful for inducing apoptosis in cells, esp. those lacking  
p53, such as cancer cells.

L3 ANSWER 2 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN

AN 2003:850077 CAPLUS <<LOGINID::20060811>>

DN 140:1482

TI Rescue of the adeno-associated virus genome from a plasmid vector:  
Evidence for rescue by replication

AU Ward, Peter; Elias, Per; Linden, R. Michael

CS Institute for Gene Therapy and Molecular Medicine, Mount Sinai School of  
Medicine, New York, NY, USA

SO Journal of Virology (2003), 77(21), 11480-11490

CODEN: JOVIAM; ISSN: 0022-538X

PB American Society for Microbiology

DT Journal

LA English

AB In cultured cells, adeno-assocd. virus (AAV) replication requires  
coinfection with a helper virus, either adenovirus or herpesvirus. In the  
absence of helper virus coinfection AAV can integrate its genome site  
specifically into the AAVS1 region of chromosome 19. Upon subsequent  
infection with a helper virus, the AAV genome is released from chromosome  
19 by a process termed rescue, and productive replication ensues. The AAV  
genome cloned into a plasmid vector can also serve to initiate productive  
AAV replication. When such constructs are transfected into cells and  
those cells are simultaneously or subsequently infected with a helper  
virus, the AAV genome is released from the plasmid. This process is  
thought to serve as a model for rescue from the human genomic site. In  
this report the authors present a model for rescue of AAV genomes by  
replication. A hallmark of this model is the prodn. of a partially  
single-stranded and partially double-stranded mol. The authors show that  
the AAV2 Rep 68 protein, together with the UL30/UL42 herpes simplex virus

type 1 DNA polymerase and the UL29 single-strand DNA binding protein ICP8, is sufficient to efficiently and precisely rescue AAV from a plasmid in a way that is dependent on the \*\*\*AAV\*\*\* \*\*\*inverted\*\*\* \*\*\*terminal\*\*\* \*\*\*repeat\*\*\* sequence.

RE.CNT 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 3 OF 11 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 1  
AN 1999328042 EMBASE <<LOGINID::20060811>>  
TI Factors affecting the terminal resolution site endonuclease, helicase, and ATPase activities of adeno-associated virus type 2 Rep proteins.  
AU Wu J.; Davis M.D.; Owens R.A.  
CS R.A. Owens, Lab. of Molec. and Cellular Biology, NIDDK, National Institutes of Health, 8 Center Dr., Bethesda, MD 20892-0840, United States. ro6n@nih.gov  
SO Journal of Virology, (1999) Vol. 73, No. 10, pp. 8235-8244. .  
Refs: 73  
ISSN: 0022-538X CODEN: JOVIAM  
CY United States  
DT Journal; Article  
FS 004 Microbiology  
LA English  
SL English  
ED Entered STN: 7 Oct 1999  
Last Updated on STN: 7 Oct 1999  
AB The Rep68 and Rep78 proteins (Rep68/78) of adeno-associated virus type 2 (AAV) are critical for AAV replication and site-specific integration. They bind specifically to the AAV inverted terminal repeats (ITRs) and possess ATPase, helicase, and strand-specific/site-specific endonuclease activities. In the present study, we further characterized the AAV Rep68/78 helicase, ATPase, and endonuclease activities by using a maltose binding protein-Rep68 fusion (MBP-Rep68.DELTA.) produced in Escherichia coli cells and Rep78 produced in vitro in a rabbit reticulocyte lysate system. We found that the minimal length of single-stranded DNA capable of stimulating the ATPase activity of MBP-Rep68.DELTA. is 100 to 200 bases. The degree of stimulation correlated positively with the length of single-stranded DNA added to the reaction mixture. We then determined the ATP concentration needed for optimal MBP-Rep68.DELTA. helicase activity and showed that the helicase is active over a wide range of ATP concentrations. We determined the directionality of MBP-Rep68.DELTA. helicase activity and found that it appears to move in a 3' to 5' direction, which is consistent with a model in which AAV Rep68/78 participates in AAV DNA replication by unwinding DNA ahead of a cellular DNA polymerase. In this report, we also demonstrate that single-stranded DNA is capable of inhibiting the MBP-Rep68.DELTA. or Rep78 endonuclease activity greater than 10-fold. In addition, we show that removal of the secondary Rep68/78 binding site, which is found only in the \*\*\*hairpin\*\*\* form of the \*\*\*AAV\*\*\* \*\*\*ITR\*\*\*, causes a three- to eightfold reduction in the ability of the ITR to be used as a substrate for the Rep78 or MBP-Rep68.DELTA. endonuclease activity. This suggests that contact between Rep68/78 and this secondary element may play an important role in the Rep-mediated endonuclease activity.

L3~ANSWER 4 OF 11 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 2  
AN 1999076497 EMBASE <<LOGINID::20060811>>  
TI Analysis of the effects of charge cluster mutations in adeno-associated virus Rep68 protein in vitro.  
AU Davis M.D.; Wonderling R.S.; Walker S.L.; Owens R.A.  
CS R.A. Owens, Lab. of Molecular/Cellular Biology, NIDDK, National Institutes of Health, 8 Center Dr. MSC 0840, Bethesda, MD 20892-0840, United States. ro6n@nih.gov  
SO Journal of Virology, (1999) Vol. 73, No. 3, pp. 2084-2093. .  
Refs: 72  
ISSN: 0022-538X CODEN: JOVIAM  
CY United States  
DT Journal; Article  
FS 004 Microbiology  
LA English  
SL English  
ED Entered STN: 19 Mar 1999  
Last Updated on STN: 19 Mar 1999  
AB The Rep78 and Rep68 proteins of adeno-associated virus type 2 (AAV) are multifunctional proteins which are required for viral replication, regulation of AAV promoters, and preferential integration of the AAV genome into a region of human chromosome 19. These proteins bind the \*\*\*hairpin\*\*\* structures formed by the \*\*\*AAV\*\*\* \*\*\*inverted\*\*\* \*\*\*terminal\*\*\* \*\*\*repeat\*\*\* ( \*\*\*ITR\*\*\* ) origins of replication, make site- and strand-specific endonuclease cuts within the AAV ITRs, and display nucleoside triphosphate-dependent helicase activities. Additionally, several mutant Rep proteins display negative dominance in helicase and/or endonuclease assays when they are mixed with wild-type Rep78 or Rep68, suggesting that multimerization may be required for the helicase and endonuclease functions. Using overlap extension PCR mutagenesis, we introduced mutations within clusters of charged residues throughout the Rep68 moiety of a maltose binding protein-Rep68 fusion protein (MBP-Rep68.DELTA.) expressed in Escherichia coli cells. Several mutations disrupted the endonuclease and helicase activities; however, only one amino-terminal- charge cluster mutant protein (D40A-D42A-D44A) completely lost AAV \*\*\*hairpin\*\*\* DNA binding activity. Charge cluster mutations within two other regions abolished both endonuclease and

helicase activities. One region contains a predicted alpha-helical structure (amino acids 371 to 393), and the other contains a putative 3,4 heptad repeat (coiled-coil) structure (amino acids 441 to 483). The defects displayed by these mutant proteins correlated with a weaker association with wild-type Rep68 protein, as measured in coimmunoprecipitation assays. These experiments suggest that these regions of the Rep molecule are involved in Rep oligomerization events critical for both helicase and endonuclease activities.

L3 ANSWER 5 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN  
AN 1998:395598 CAPLUS <<LOGINID::20060811>>  
DN 129:131773  
TI Characterization of wild-type adeno-associated virus type 2-like particles generated during recombinant viral vector production and strategies for their elimination  
AU Wang, Xu-Shan; Khuntirat, Benjawan; Qing, Keyun; Ponnazhagan, Selvarangan;  
Kube, Dagmar M.; Zhou, Shangzhen; Dwarki, Varavani J.; Srivastava, Arun  
CS Department of Microbiology and Immunology, Indiana University School of Medicine, Indianapolis, IN, 46202, USA  
SO Journal of Virology (1998), 72(7), 5472-5480  
CODEN: JOVIAM; ISSN: 0022-538X  
PB American Society for Microbiology  
DT Journal  
LA English  
AB The pSub201-pAAV/Ad plasmid cotransfection system was developed to eliminate homologous recombination which leads to generation of the wild-type (wt) adeno-assocd. virus type 2 (AAV) during recombinant vector prodn. The extent of contamination with wt AAV has been documented to range between 0.01 and 10%. However, the precise mechanism of generation of the contaminating wt AAV remains unclear. To characterize the wt AAV genomes, recombinant viral stocks were used to infect human 293 cells in the presence of adenovirus. Southern blot analyses of viral replicative DNA intermediates revealed that the contaminating AAV genomes were not authentic wt but rather wt AAV-like sequences derived from recombination between (i) AAV inverted terminal repeats (ITRs) in the recombinant plasmid and (ii) AAV sequences in the helper plasmid. Replicative AAV DNA fragments, isolated following amplification through four successive rounds of amplification in adenovirus-infected 293 cells, were molecularly cloned and subjected to nucleotide sequencing to identify the recombinant junctions. Following sequence analyses of 31 different ends of AAV-like genomes derived from two different recombinant vector stocks, we obsd. that all recombination events involved 10 nucleotides in the AAV D sequence distal to viral \*\*\*hairpin\*\*\* structures. We have recently documented that the first 10 nucleotides in the D sequence proximal to the AAV \*\*\*hairpin\*\*\* structures are essential for successful replication and encapsidation of the viral genome (X.-S. Wang et al., J. Virol. 71:3077-3082, 1997), and it was noteworthy that in each recombinant junction sequenced, the same 10 nucleotides were retained. We also obsd. that adenovirus ITRs in the helper plasmid were involved in illegitimate recombination with AAV ITRs, deletions of which significantly reduced the extent of wt AAV-like particles. Furthermore, the combined use of recombinant AAV plasmids lacking the distal 10 nucleotides in the D sequence and helper plasmids lacking the adenovirus ITRs led to complete elimination of replication-competent wt AAV-like particles in recombinant vector stocks. These strategies should be useful in producing clin.-grade AAV vectors suitable for human gene therapy.

RE.CNT 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 6 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN  
AN 1997:185237 CAPLUS <<LOGINID::20060811>>  
DN 126:260047  
TI Adeno-associated virus type 2 DNA replication in vivo: mutation analyses of the D sequence in viral inverted terminal repeats  
AU Wang, Xu-Shan; Qing, Keyun; Ponnazhagan, Selvarangan; Srivastava, Arun  
CS Dep. Med., Indiana Univ. Sch. Med., Indianapolis, IN, 46202, USA  
SO Journal of Virology (1997), 71(4), 3077-3082  
CODEN: JOVIAM; ISSN: 0022-538X  
PB American Society for Microbiology  
DT Journal  
LA English  
AB The adeno-assocd. virus type 2 (AAV) genome contains inverted terminal repeats (ITRs) of 145 nucleotides. The terminal 126 nucleotides of each ITR form palindromic \*\*\*hairpin\*\*\* (HP) structures that serve as primers for AAV DNA replication. These HP structures also play an important role in integration as well as rescue of the proviral genome from latently infected cells or from recombinant AAV plasmids. Each ITR also contains a stretch of 20 nucleotides, designated the D sequence, that is not involved in HP structure formation. We have recently shown that the D sequence plays a crucial role in high-efficiency rescue, selective replication, and encapsidation of the AAV genome and that a host cell protein, designated the D sequence-binding protein (D-BP), specifically interacts with this sequence (X.-S. Wang, S. Ponnazhagan, and A. Srivastava, J. Virol. 70:1668-1677, 1996). We have now performed mutational analyses of the D sequences to evaluate their precise role in viral DNA rescue, replication, and packaging. We report here that 10 nucleotides proximal to the HP structure in each of the D sequences are necessary and sufficient to mediate high-efficiency rescue, replication, and encapsidation of the viral genome in vivo. In *in vitro* studies, the same 20 nucleotides were found to be required for specific interaction with D-BP, but viral Rep protein-mediated cleavage at the functional

terminal resolv. site is independent of these sequences. These data suggest that AAV replication and terminal resolv. functions can be uncoupled and that the lack of efficient replication of AAV DNA may not be a consequence of impaired resolv. of the viral ITRs. These studies further illustrate that the D sequence-D-BP interaction plays an important role in the AAV life cycle and indicate that it may be possible to develop the next generation of AAV vectors capable of encapsidating larger pieces of DNA.

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AN 97022439 EMBASE <<LOGINID::20060811>>

DN 1997022439

TI A novel terminal resolution-like site in the adeno-associated virus type 2 genome.

AU Wang X.-S.; Srivastava A.

CS A. Srivastava, Dept. of Microbiology and Immunology, Medical Science Building, Indiana Univ. School of Medicine, 635 Barnhill Dr., Indianapolis, IN 46202-5120, United States

SO Journal of Virology, (1997) Vol. 71, No. 2, pp. 1140-1146. .

Refs: 36

ISSN: 0022-538X CODEN: JOVIAM

CY United States

DT Journal; Article

FS 004 Microbiology

LA English

SL English

ED Entered STN: 15 Feb 1997

Last Updated on STN: 15 Feb 1997

AB The adeno-associated virus 2 (AAV) contains a single-stranded DNA genome of which the terminal 145 nucleotides are palindromic and form T-shaped \*\*\*hairpin\*\*\* structures. These inverted terminal repeats (ITRs) play an important role in AAV DNA replication and resolution, since each of the ITRs contains a terminal resolution site (trs) that is the target site for the AAV rep gene products (Rep). However, the Rep proteins also interact with the AAV DNA sequences that lie outside the ITRs, and the ITRs also play a crucial role in excision of the proviral genome from latently infected cells or from recombinant AAV plasmids. To distinguish between Rep-mediated excision of the viral genome during rescue from recombinant AAV plasmids and the Rep-mediated resolution of the ITRs during AAV DNA replication, we constructed recombinant AAV genomes that lacked either the left or the right ITR sequence and one of the Rep-binding sites (RBSs). No rescue and replication of the AAV genome occurred from these plasmids following transfection into adenovirus type 2- infected human KB cells, as expected. However, excision and abundant replication of the vector sequences was clearly detected from the plasmid that lacked the \*\*\*AAV\*\*\* left \*\*\*ITR\*\*\*, suggesting the existence of an additional putative excision site in the left end of the AAV genome. This site was precisely mapped to one of the AAV promoters at map unit 5 (AAV p5) that also contains an RBS. Furthermore, deletion of this RBS abolished the rescue and replication of the vector sequences. These studies suggest that the Rep-mediated cleavage at the RBS during viral DNA replication may, in part, account for the generation of the AAV defective interfering particles.

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AN 97021985 EMBASE <<LOGINID::20060811>>

DN 1997021985

TI A novel 165-base-pair terminal repeat sequence is the sole cis requirement for the adeno-associated virus life cycle.

AU Xiao X.; Xiao W.; Li J.; Samulski R.J.

CS R.J. Samulski, Department of Pharmacology, Gene Therapy Center, University of North Carolina, Chapel Hill, NC 27599, United States. rjs@med.unc.edu

SO Journal of Virology, (1997) Vol. 71, No. 2, pp. 941-948. .

Refs: 50

ISSN: 0022-538X CODEN: JOVIAM

CY United States

DT Journal; Article

FS 004 Microbiology

LA English

SL English

ED Entered STN: 15 Feb 1997

Last Updated on STN: 15 Feb 1997

AB Adeno-associated virus (AAV) replication is dependent on two copies of a 145-bp inverted terminal repeat ( \*\*\*ITR\*\*\* ) that flank the \*\*\*AAV\*\*\* genome. This is the primary cis-acting element required for productive infection and the generation of recombinant AAV (rAAV) vectors. We have engineered a plasmid (pDD-2) containing only 165 bp of AAV sequence: two copies of the D element, a unique sequence adjacent to the AAV nicking site, flanking a single ITR. When assayed in vivo, this modified \*\*\*hairpin\*\*\* was sufficient for the replication of the plasmid vector when Rep and adenovirus (Ad) helper functions were supplied in trans. pDD-2 replication intermediates were characteristic of the AAV replication scheme in which linear monomer, dimer, and other higher-molecular-weight replicative intermediates are generated. Compared to infectious AAV clones for replication, the modified \*\*\*hairpin\*\*\* vector replicated more efficiently independent of size. Further analysis demonstrated conversion of the input circular plasmid to a linear substrate with AAV

terminal repeat elements at either end as an initial step for replication. This conversion was independent of both Rep and Ad helper genes, suggesting the role of host factors in the production of these molecules. The generation of these substrates suggested resolution of the modified terminal repeat through a Holliday-like structure rather than replication as a mechanism for rescue. Production of replicative intermediates via this plasmid substrate were competent not only for AAV DNA replication but also for encapsidation, infection, integration, and subsequent rescue from the chromosome when superinfected with Ad and wild-type AAV. These studies demonstrate that this novel 165-bp ITR substrate is sufficient in cis for the AAV life cycle and should provide a valuable reagent for further dissecting the cis sequences involved in AAV replication, packaging, and integration. In addition, this novel plasmid vector can be used as a substrate for both rAAV vector production and synthetic plasmid vector delivery.

L3 ANSWER 9 OF 11 CAPLUS COPYRIGHT 2006 ACS ON STN

AN 1995:722338 CAPLUS <<LOGINID::20060811>>

DN 123:162648

TI Rescue and replication signals of the adeno-associated virus 2 genome

AU Wang, Xu-Shan; Ponnazhagan, Selvarangan; Srivastava, Arun  
CS Div. Hematol./Oncol., Indiana Univ. Sch. Med., Indianapolis, IN, 46202-5120, USA

SO Journal of Molecular Biology (1995), 250(5), 573-80

CODEN: JMOBAK; ISSN: 0022-2836

PB Academic

DT Journal

LA English

AB The adeno-assocd. virus 2 (AAV) genome is a single-stranded DNA which contains the inverted terminal repeats (ITRs) of 145 nucleotides. The terminal 125 nucleotides of each ITR form palindromic \*\*\*hairpin\*\*\* structures that serve as primers for AAV DNA replication. These \*\*\*hairpin\*\*\* structures also play a crucial role in the integration, as well as the rescue, of the proviral genome from latently-infected cells, or from the recombinant AAV plasmids. However, the ITRs also contain an addnl. domain, designated the D-sequence, a 20-nucleotide stretch that is not involved in the formation of hairpins. In order to examine the role of the D-sequence in viral DNA rescue and replication, a no. of recombinant AAV plasmids were constructed which contained deletions/substitutions in different regions of the ITRs. The results presented here reveal the existence of addnl. sequences, other than the \*\*\*hairpin\*\*\* structures, which serve as primers for AAV DNA replication. The results also show that whereas the \*\*\*hairpin\*\*\* structures are sufficient for excision and replication of the viral DNA, the D-sequence is crucial for the high efficiency of rescue and replication of the AAV genome.

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AN 94029084 EMBASE <<LOGINID::20060811>>

DN 1994029084

TI Biologically active Rep proteins of adeno-associated virus type 2 produced as fusion proteins in Escherichia coli.

AU Chiorini J.A.; Weitzman M.D.; Owens R.A.; Urcelay E.; Safer B.; Kotin R.M.

CS Molecular Hematology Branch, National Heart, Lung/Blood Institute, National Institutes of Health, Bethesda, MD 20892, United States

SO Journal of Virology, (1994) Vol. 68, No. 2, pp. 797-804. .

ISSN: 0022-538X CODEN: JOVIAM

CY United States

DT Journal; Article

FS 004 Microbiology

LA English

SL English

ED Entered STN: 6 Feb 1994

Last Updated on STN: 6 Feb 1994

AB Four Rep proteins are encoded by the human parvovirus adeno-associated virus type 2 (AAV). The two largest proteins, Rep68 and Rep78, have been shown in vitro to perform several activities related to AAV DNA replication. The Rep78 and Rep68 proteins are likely to be involved in the targeted integration of the AAV DNA into human chromosome 19, and the full characterization of these proteins is important for exploiting this phenomenon for the use of AAV as a vector for gene therapy. To obtain sufficient quantities for facilitating the characterization of the biochemical properties of the Rep proteins, the AAV rep open reading frame was cloned and expressed in Escherichia coli as a fusion protein with maltose-binding protein (MBP). Recombinant MBP-Rep68 and MBP-Rep78 proteins displayed the following activities reported for wild-type Rep proteins when assayed in vitro: (i) binding to the \*\*\*AAV\*\*\* \*\*\*inverted\*\*\* \*\*\*terminal\*\*\* \*\*\*repeat\*\*\* ( \*\*\*ITR\*\*\* ), (ii) helicase activity, (iii) site-specific (terminal resolution site) endonuclease activity, (iv) binding to a sequence within the integration locus for AAV DNA on human chromosome 19, and (v) stimulation of radiolabeling of DNA containing the \*\*\*AAV\*\*\* \*\*\*ITR\*\*\* in a cell extract. These five activities have been described for wild-type Rep produced from mammalian cell extracts. Furthermore, we recharacterized the sequence requirements for Rep binding to the ITR and found that only the A and A' regions are necessary, not the \*\*\*hairpin\*\*\* form of the ITR.

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AN 89156065 EMBASE <<LOGINID::20060811>>

DN 1989156065

TI Identification of nuclear proteins that specifically interact with adeno-associated virus type 2 inverted terminal repeat \*\*\*hairpin\*\*\* DNA.

AU Ashktorab H.; Srivastava A.

CS Division of Hematology and Oncology, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN 46202, United States

SO Journal of Virology, (1989) Vol. 63, No. 7, pp. 3034-3039.

ISSN: 0022-538X CODEN: JOVIAM

CY United States

DT Journal

FS 047 Virology

LA English

SL English

ED Entered STN: 12 Dec 1991

Last Updated on STN: 12 Dec 1991

AB A palindromic \*\*\*hairpin\*\*\* duplex containing the inverted terminal repeat sequence of adeno-associated virus type 2 (AAV) DNA was used as a substrate in gel retardation assays to detect putative proteins that specifically interact with the AAV \*\*\*hairpin\*\*\* DNA structures. Nuclear proteins were detected in extracts prepared from human KB cells cotransfected with AAV and adenovirus type 2 that interacted with the \*\*\*hairpin\*\*\* duplex but not in nuclear extracts prepared from uninfected, AAV-infected, or adenovirus type 2-infected KB cells. The binding was specific for the \*\*\*hairpin\*\*\* duplex, since no binding occurred with a double-stranded DNA duplex with the identical nucleotide sequence. S1 nuclease assays revealed that the binding was sensitive to digestion with the enzyme, whereas the protein-bound \*\*\*hairpin\*\*\* duplex was resistant to digestion with S1 nuclease. The nucleotide sequence involved in the protein binding was localized within the \*\*\*inverted\*\*\* \*\*\*terminal\*\*\* \*\*\*repeat\*\*\* of the \*\*\*AAV\*\*\* genome by methylation interference assays. These nuclear proteins may be likely candidates for the pivotal enzyme nickase required for replication or resolution (or both) of single-stranded palindromic \*\*\*hairpin\*\*\* termini of the AAV genome.

=> d his

(FILE 'HOME' ENTERED AT 15:31:24 ON 11 AUG 2006)

FILE 'EMBASE, BIOSIS, CAPLUS' ENTERED AT 15:31:41 ON 11 AUG 2006

FILE 'EMBASE, BIOSIS, CAPLUS' ENTERED AT 15:31:55 ON 11 AUG 2006

L1 178 S AAV (3A) (ITR OR INVERT? TERMINAL REPEAT)

L2 23 S L1 AND HAIRPIN

L3 11 DUP REM L2 (12 DUPLICATES REMOVED)

=> s kissing ear

L4 0 KISSING EAR

=> s kiss? ear

L5 0 KISS? EAR

=> s AAV

L6 6199 AAV

=> s l6 and hairpin

L7 154 L6 AND HAIRPIN

=> s l7 not l2

L8 131 L7 NOT L2

=> dup rem l8

PROCESSING COMPLETED FOR L8

L9 61 DUP REM L8 (70 DUPLICATES REMOVED)

=> d bib abs

L9 ANSWER 1 OF 61 CAPLUS COPYRIGHT 2006 ACS on STN

AN 2006:15085 CAPLUS <<LOGINID::20060811>>

DN 144:101995

TI Adeno-associated virus vector systems and methods for delivering biologically active agents to cells across a blood-brain barrier

IN Kaemmerer, William F.; Burright, Eric N.; Tenbroek, Erica M.; Blum, Janelle L.; Kaytor, Michael D.

PA Medtronic, Inc., USA

SO PCT Int. Appl., 104 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 4

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI WO 2006002283	A1	20060105	WO 2005-US22156	20050621
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WO 2006002283	C2	20060420		
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W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GR, GU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK,

SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU,

ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF,

CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG,

KZ, MD, RU, TJ, TM

US 2006018882 A1 20060126 US 2005-157608 20050621

PRAI US 2004-581730P P 20040621

AB The present invention provides a medical system for delivering DNA encoding a biol. active agent across a blood-brain barrier. In one embodiment, the system includes: a neurovascular catheter having a distal end positioned in a blood vessel supplying a patient's brain; and a means for delivering to the catheter a compn. including: an artificial adeno-assocd. virus ( \*\*\*AAV\*\*\* ) vector including DNA encoding a biol. active agent; and a component to deliver at least the DNA across the blood-brain barrier. In another embodiment, the system includes a neurovascular catheter having a distal end positioned in a blood vessel supplying a patient's brain; and a means for delivering to the catheter a compn. including a receptor-specific liposome, wherein the receptor-specific liposome includes: a liposome having an exterior surface and an internal compartment; an artificial adeno-assocd. virus ( \*\*\*AAV\*\*\* ) vector located within the internal compartment of the liposome, wherein the \*\*\*AAV\*\*\* vector includes DNA encoding a biol. active agent; one or more blood-brain barrier and brain cell membrane targeting agents; and one or more conjugation agents wherein each targeting agent is connected to the exterior surface of the liposome via at least one of the conjugation agents. In another aspect, the present invention provides a method for delivering DNA across a blood-brain barrier for expression in the brain. In another aspect, the present invention provides a method of treating a neurodegenerative disorder caused by a pathogenic protein. In another aspect, the present invention provides a compn. for delivering DNA across a blood-brain barrier for expression in the brain. The present invention can offer advantages over other methods of delivering biol. active agents including, for example, conventional enhanced delivery, stereotactic neurosurgical delivery of viral or nonviral vectors, and/or i.v. delivery of a compn. for carrying plasmid DNA or RNA across the blood brain barrier. The use of an artificial \*\*\*AAV\*\*\* vector to deliver a gene or a gene-suppressing agent to a patient's brain can have many advantages over the delivery of plasmid DNA, or the delivery of actual \*\*\*AAV\*\*\* virus particles.

RE.CNT 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d bib abs 2-20

L9 ANSWER 2 OF 61 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

DUPLICATE 1

AN 2006323626 EMBASE <<LOGINID::20060811>>

TI \*\*\*AAV\*\*\* delivery of mineralocorticoid receptor shRNA prevents progression of cold-induced hypertension and attenuates renal damage.

AU Wang X.; Skelley L.; Cade R.; Sun Z.

CS Dr. Z. Sun, Department of Medicine, College of Medicine, University of Florida, 1600 SW Archer Road, Gainesville, FL 32610-0274, United States.

zsun@phys.med.ufl.edu

SO Gene Therapy, (2006) Vol. 13, No. 14, pp. 1097-1103.

Refs: 43

ISSN: 0969-7128 E-ISSN: 1476-5462 CODEN: GETHEC

PUI 3302768

CY United Kingdom

DT Journal; Article

FS 004 Microbiology

018 Cardiovascular Diseases and Cardiovascular Surgery

022 Human Genetics

028 Urology and Nephrology

037 Drug Literature Index

LA English

SL English

ED Entered STN: 26 Jul 2006

Last Updated on STN: 26 Jul 2006

AB The aim of this study was to determine the effect of RNA interference inhibition of mineralocorticoid receptor (MR) on cold-induced hypertension (CIH) and renal damage. Recombinant adeno-associated virus ( \*\*\*AAV\*\*\* ) carrying short \*\*\*hairpin\*\*\* small interference (si)RNA for MR ( \*\*\*AAV\*\*\* .MR-shRNA) was constructed and tested for the ability to inhibit renal MR and to control CIH. Three groups of rats with CIH received \*\*\*AAV\*\*\* .MR-shRNA (1.25 x 10<sup>9</sup> particles/rat, intravenous), \*\*\*AAV\*\*\* carrying scrambled shRNA ( \*\*\*AAV\*\*\* .Control-shRNA) (1.25 x 10<sup>9</sup> particles/rat, intravenous) and phosphate buffer solution (PBS), respectively. All rats were kept in a cold chamber (6.7.degree.C) throughout the experiment. Adeno-associated virus delivery of MR-shRNA prevented progression of CIH. Blood pressure (BP) of the \*\*\*AAV\*\*\* .MR-shRNA-treated group did not increase and remained at 145 +/- 3 mm Hg, whereas BP of the \*\*\*AAV\*\*\* .Control-shRNA-treated and PBS-treated group increased to 167 +/- 4 and 161 +/- 3 mm Hg, respectively, at 3 weeks after gene delivery. Thus, the antihypertensive effect of a single injection of \*\*\*AAV\*\*\* .MR-shRNA lasted for at least 3 weeks (length of the study). Adeno-associated virus carrying short \*\*\*hairpin\*\*\* siRNA for MR significantly increased urinary sodium excretion and decreased proteinuria. It also decreased serum creatinine and blood urea nitrogen, suggesting enhanced renal function. Both Western blot and

immunohistochemical analysis showed that MR expression was decreased significantly in the kidney in the \*\*\*AAV\*\*\*.MR-shRNA-treated rats, confirming that renal MR is effectively inhibited by \*\*\*AAV\*\*\*.MR-shRNA. Adeno-associated virus carrying short \*\*\*hairpin\*\*\* siRNA for MR also significantly attenuated renal hypertrophy. In addition, \*\*\*AAV\*\*\* delivery of MR-shRNA prevented atrophy and dilation of renal tubules and abolished tubular deposition of proteinaceous material seen in CIH rats. Conclusions: (1) \*\*\*AAV\*\*\* delivery of MR-shRNA effectively silenced MR in vivo. (2) RNA interference inhibition of MR may open a new avenue for the long-term control of hypertension and renal damage. .COPYRG.T. 2006 Nature Publishing Group All rights reserved.

L9 ANSWER 3 OF 61 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 2

AN 2006335967 EMBASE <<LOGINID:20060811>>

TI Fatality in mice due to oversaturation of cellular microRNA/short \*\*\*hairpin\*\*\* RNA pathways.

AU Grimm D.; Streetz K.L.; Jopling C.L.; Storm T.A.; Pandey K.; Davis C.R.; Marion P.; Salazar F.; Kay M.A.

CS M.A. Kay, Stanford University, School of Medicine, Departments of Pediatrics and Genetics, Stanford, CA 94305, United States. markay@stanford.edu

SO Nature, (25 May 2006) Vol. 441, No. 7092, pp. 537-541. .

Refs: 30

ISSN: 0028-0836 E-ISSN: 1476-4679 CODEN: NATUAS

PUI NATURE04791

CY United Kingdom

DT Journal; Article

FS 004 Microbiology

022 Human Genetics

037 Drug Literature Index

LA English

SL English

ED Entered STN: 31 Jul 2006

Last Updated on STN: 31 Jul 2006

AB RNA interference (RNAi) is a universal and evolutionarily conserved phenomenon of post-transcriptional gene silencing by means of sequence-specific mRNA degradation, triggered by small double-stranded RNAs. Because this mechanism can be efficiently induced in vivo by expressing target-complementary short \*\*\*hairpin\*\*\* RNA (shRNA) from non-viral and viral vectors, RNAi is attractive for functional genomics and human therapeutics. Here we systematically investigate the long-term effects of sustained high-level shRNA expression in livers of adult mice. Robust shRNA expression in all the hepatocytes after intravenous infusion was achieved with an optimized shRNA delivery vector based on duplex-DNA-containing adeno-associated virus type 8 (AAV8). An evaluation of 49 distinct \*\*\*AAV\*\*\* /shRNA vectors, unique in length and sequence and directed against six targets, showed that 36 resulted in dose-dependent liver injury, with 23 ultimately causing death. Morbidity was associated with the downregulation of liver-derived microRNAs (miRNAs), indicating possible competition of the latter with shRNAs for limiting cellular factors required for the processing of various small RNAs. In vitro and in vivo shRNA transfection studies implied that one such factor, shared by the shRNA/miRNA pathways and readily saturated, is the nuclear karyopherin exportin-5. Our findings have fundamental consequences for future RNAi-based strategies in animals and humans, because controlling intracellular shRNA expression levels will be imperative. However, the risk of oversaturating endogenous small RNA pathways can be minimized by optimizing shRNA dose and sequence, as exemplified here by our report of persistent and therapeutic RNAi against human hepatitis B virus in vivo. .COPYRG.T. 2006 Nature Publishing Group.

L9 ANSWER 4 OF 61 CAPLUS COPYRIGHT 2006 ACS on STN

AN 2005:1223690 CAPLUS <<LOGINID:20060811>>

DN 143:472607

TI Nucleic acid silencing of Huntington's disease gene

IN Davidson, Beverly L.; Harper, Scott

PA University of Iowa Research Foundation, USA

SO U.S. Pat. Appl. Publ., 106 pp., Cont.in-part of U.S. Ser. No. 859,751.

CODEN: USXXCO

DT Patent

LA English

FAN.CNT 5

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2005255086	A1	20051117	US 2005-48627	20050131
US 2005106731	A1	20050519	US 2002-212322	20020805
US 2004023390	A1	20040205	US 2003-430351	20030505
WO 2004013280	A2	20040212	WO 2003-US16887	20030526
WO 2004013280	A3	20051229		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004241854	A1	20041202	US 2003-738642	20031216
US 2005042646	A1	20050224	US 2004-859751	20040602
AU 2005200828	A1	20050317	AU 2005-200828	20050224

WO 2006031267 A2 20060323 WO 2005-US19749 20050602  
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

WO 2006083800 A2 20060810 WO 2006-US3298 20060131  
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRAI US 2002-212322 A2 20020805

US 2002-322086 B1 20021217

US 2003-430351 A2 20030505

WO 2003-US16887 A2 20030526

US 2003-738642 A2 20031216

US 2004-859751 A2 20040602

AU 2003-251383 A3 20030526

US 2005-48627 A 20050131

AB The invention is directed to small interfering RNA moles. (siRNA) targeted against a Huntington's Disease gene, and methods of using these siRNA moles.

L9 ANSWER 5 OF 61 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 3

AN 2005378269 EMBASE <<LOGINID:20060811>>

TI The cellular TATA binding protein is required for Rep-dependent replication of a minimal adeno-associated virus type 2 p5 element.

AU Francois A.; Guilbaud M.; Awedikian R.; Chadeuf G.; Moullier P.; Salvetti A.

CS A. Salvetti, Laboratoire de Therapie Genique, INSERM U649, CHU Hotel Dieu, 30 Bd Jean Monnet, 44035 Nantes Cedex 1, France. anna.salvetti@univ-nantes.fr

SO Journal of Virology, (2005) Vol. 79, No. 17, pp. 11082-11094. .

Refs: 68

ISSN: 0022-538X CODEN: JOVIAM

CY United States

DT Journal; Article

FS 004 Microbiology

LA English

SL English

ED Entered STN: 15 Sep 2005

Last Updated on STN: 15 Sep 2005

AB The p5 promoter region of adeno-associated virus type 2 ( \*\*\*AAV\*\*\* -2) is a multifunctional element involved in rep gene expression, Rep-dependent replication, and site-specific integration. We initially characterized a 350-bp p5 region by its ability to behave like a cis-acting replication element in the presence of Rep proteins and adenoviral factors. The objective of this study was to define the minimal elements within the p5 region required for Rep-dependent replication. Assays performed in transfected cells (in vivo) indicated that the minimal p5 element was composed by a 55-bp sequence (nucleotides 250 to 304 of wild-type \*\*\*AAV\*\*\* -2) containing the TATA box, the Rep binding site, the terminal resolution site present at the transcription initiation site (trs(+1)), and a downstream 17-bp region that could potentially form a \*\*\*hairpin\*\*\* structure localizing the trs(+1) at the top of the loop. Interestingly, the TATA box was absolutely required for in vivo but dispensable for in vitro, i.e., cell-free, replication. We also demonstrated that Rep binding and nicking at the trs(+1) was enhanced in the presence of the cellular TATA binding protein, and that overexpression of this cellular factor increased in vivo replication of the minimal p5 element. Together, these studies identified the minimal replication origin present within the \*\*\*AAV\*\*\* -2 p5 promoter region and demonstrated for the first time the involvement of the TATA box, in cis, and of the TATA binding protein, in trans, for Rep-dependent replication of this viral element. Copyright .COPYRG.T. 2005, American Society for Microbiology. All Rights Reserved.

L9 ANSWER 6 OF 61 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 4

AN 2005220892 EMBASE <<LOGINID:20060811>>

TI Effects of adeno-associated virus DNA \*\*\*hairpin\*\*\* structure on recombination.

AU Choi V.W.; Samulski R.J.; McCarty D.M.

CS R.J. Samulski, 7119 Thurston Bowles, CB 7352, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, United States. rjs@med.unc.edu

SO Journal of Virology, (2005) Vol. 79, No. 11, pp. 6801-6807. .



Refs: 38  
ISSN: 0022-538X CODEN: JOVIAM  
CY United States  
DT Journal; Article  
FS 004 Microbiology  
LA English  
SL English  
ED Entered STN: 16 Jun 2005  
Last Updated on STN: 16 Jun 2005

AB \*\*\*Hairpin\*\*\* DNA ends are evolutionarily conserved intermediates in DNA recombination. The \*\*\*hairpin\*\*\* structures present on the ends of the adeno-associated virus ( \*\*\*AAV\*\*\* ) genome are substrates for recombination that give rise to persistent circular and concatemeric DNA episomes through intramolecular and intermolecular recombination, respectively. We have developed circularization-dependent and orientation-specific self-complementary \*\*\*AAV\*\*\* (scAAV) vectors as a reporter system to examine recombination events involving distinct \*\*\*hairpin\*\*\* structures, i.e., closed versus open hairpins. The results suggest that intramolecular recombination (circularization) is far more efficient than intermolecular recombination (concatemerization). Among all possible combinations of terminal repeats (TRs) involved in intermolecular recombination, the closed-closed TR structures are twice as efficient as the open-open TR substrates for recombination. In addition, both intramolecular recombination and intermolecular recombination exhibit the common dependency on specific DNA polymerases and topoisomerases. The circularization-dependent and orientation-specific scAAV vectors can serve as an efficient and controlled system for the delivery of DNA structures that mimic mammalian recombination intermediates and should be useful in assaying recombination in different experimental settings as well as elucidating the molecular mechanism of recombinant \*\*\*AAV\*\*\* genome persistence. Copyright .COPYRG. 2005, American Society for Microbiology. All Rights Reserved.

L9 ANSWER 7 OF 61 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN  
AN 2005327715 EMBASE <<LOGINID:20060811>>  
TI Stable inhibition of hepatitis B virus proteins by small interfering RNA expressed from viral vectors.  
AU Moore M.D.; McGarvey M.J.; Russell R.A.; Cullen B.R.; McClure M.O.  
CS M.O. McClure, Jefferiss Trust Laboratories, Wright-Fleming Institute, Imperial College London, London, United Kingdom. m.mcclure@imperial.ac.uk  
SO Journal of Gene Medicine, (2005) Vol. 7, No. 7, pp. 918-925. .  
Refs: 45  
ISSN: 1099-498X CODEN: JGMEFG  
CY United Kingdom  
DT Journal; Article  
FS 004 Microbiology  
005 General Pathology and Pathological Anatomy  
022 Human Genetics  
037 Drug Literature Index  
039 Pharmacy  
048 Gastroenterology  
LA English  
SL English  
ED Entered STN: 5 Aug 2005  
Last Updated on STN: 5 Aug 2005

AB Background: There has been much research into the use of RNA interference (RNAi) for the treatment of human diseases. Many viruses, including hepatitis B virus (HBV), are susceptible to inhibition by this mechanism. However, for RNAi to be effective therapeutically, a suitable delivery system is required. Methods: Here we identify an RNAi sequence active against the HBV surface antigen (HBsAg), and demonstrate its expression from a polymerase III expression cassette. The expression cassette was inserted into two different vector systems, based on either prototype foamy virus (PFV) or adeno-associated virus ( \*\*\*AAV\*\*\* ), both of which are non-pathogenic and capable of integration into cellular DNA. The vectors containing the HBV-targeted RNAi molecule were introduced into 293T.HBs cells, a cell line stably expressing HBsAg. The vectors were also assessed in HepG2.2.15 cells, which secrete infectious HBV virions. Results: Seven days post-transduction, a knockdown of HBsAg by approximately 90%, compared with controls, was detected in 293T.HBs cells transduced by shRNA encoding PFV and \*\*\*AAV\*\*\* vectors. This reduction has been observed up to 5 months post-transduction in single cell clones. Both vectors successfully inhibited HBsAg expression from HepG2.2.15 cells even in the presence of HBV replication. RT-PCR of RNA extracted from these cells showed a reduction in the level of HBV pre-genomic RNA, an essential replication intermediate and messenger RNA for HBV core and polymerase proteins, as well as the HBsAg messenger RNA. Conclusions: This work is the first to demonstrate that delivery of RNAi by viral vectors has therapeutic potential for chronic HBV infection and establishes the ground work for the use of such vectors in vivo. Copyright .COPYRG. 2005 John Wiley & Sons, Ltd.

L9 ANSWER 8 OF 61 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN  
AN 2005234313 EMBASE <<LOGINID:20060811>>  
TI In vivo inhibition of hippocampal Ca(2+)/calmodulin-dependent protein kinase II by RNA interference.  
AU Babcock A.M.; Standing D.; Bullshields K.; Schwartz E.; Paden C.M.; Poulsen D.J.  
CS A.M. Babcock, Department of Psychology, Montana State University, Bozeman,

MT 59717, United States. mbabcock@montana.edu  
SO Molecular Therapy, (2005) Vol. 11, No. 6, pp. 899-905. .

Refs: 32  
ISSN: 1525-0016 CODEN: MTOHCK  
PUI S 1525-0016(05)00088-9  
CY United States  
DT Journal; Article  
FS 008 Neurology and Neurosurgery  
022 Human Genetics  
030 Pharmacology  
037 Drug Literature Index  
039 Pharmacy  
LA English  
SL English  
ED Entered STN: 9 Jun 2005  
Last Updated on STN: 9 Jun 2005

AB Hippocampal .alpha.-Ca(2+)/calmodulin-dependent protein kinase II (.alpha.-CaMKII) has been implicated in spatial learning, neuronal plasticity, epilepsy, and cerebral ischemia. In the present study, an adeno-associated virus ( \*\*\*AAV\*\*\* ) vector was designed to express green fluorescent protein (GFP) from the CBA promoter and a small \*\*\*hairpin\*\*\* RNA targeting .alpha.-CaMKII ( \*\*\*AAV\*\*\* -shCAM) driven from the U6 promoter. The \*\*\*AAV\*\*\* -shCAM or control vector was microinfused into the rat hippocampus and behavioral testing conducted 19-26 days following surgery. Expression of the marker gene and .alpha.-CaMKII was evaluated 31 days following \*\*\*AAV\*\*\* infusion. GFP expression was localized to the hippocampus and extended .+-.2 mm rostral and caudal from the injection site. Hippocampal .alpha.-CaMKII was significantly reduced following \*\*\*AAV\*\*\* -shCAM treatment as demonstrated using immunohistochemical and Western analysis. This suppression of .alpha.-CaMKII was associated with changes in exploratory behavior (open field task) and impaired place learning (water maze task). These results demonstrate the efficacy of a viral-based delivered shRNA to produce gene suppression in a specific circuit of the brain. Copyright .COPYRG. The American Society of Gene Therapy.

L9 ANSWER 9 OF 61 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN  
AN 2005028550 EMBASE <<LOGINID:20060811>>  
TI Adeno-associated virus vectors for short \*\*\*hairpin\*\*\* RNA expression.  
AU Grimm D.; Pandey K.; Kay M.A.  
SO Methods in Enzymology, (2005) Vol. 392, pp. 381-405. .

Refs: 42  
ISSN: 0076-6879 CODEN: MENZAU  
PUI S 0076-6879(04)92023-X  
CY United States  
DT Journal; General Review  
FS 022 Human Genetics  
LA English  
SL English  
ED Entered STN: 4 Feb 2005  
Last Updated on STN: 4 Feb 2005

AB Five recent publications have documented the successful development and use of gene transfer vectors based on adeno-associated virus ( \*\*\*AAV\*\*\* ) for expressing short \*\*\*hairpin\*\*\* RNA (shRNA). In cultured mammalian cells and in whole animals, infection with these vectors was shown to result in specific, efficient, and stable knockdown of various targeted endo- or exogenous genes. Here we review this exciting approach, to trigger RNA interference in vitro and in vivo by shRNA expressed from \*\*\*AAV\*\*\* vectors, and describe the state-of-the-art technology for vector particle generation. In particular, we present a set of novel \*\*\*AAV\*\*\* vector plasmids that were specifically designed for the easy and rapid cloning of shRNA expression cassettes into \*\*\*AAV\*\*\* . The plasmids contain alternative RNA polymerase III promoters (U6, H1, or 7SK) together with a respective terminator sequence, as well as stuffer DNA to guarantee an optimal vector size for efficient packaging into \*\*\*AAV\*\*\* capsids. To provide maximum versatility and user-friendliness, the constructs were also engineered to contain a set of unique restriction enzyme recognition sites, allowing the simple and straightforward replacement of the shRNA cassette or other vector components with customized sequences. Our novel vector plasmids complement existing \*\*\*AAV\*\*\* vector technology and should help further establish \*\*\*AAV\*\*\* as a most promising alternative to using adeno- or retro-/lentiviral vectors as shRNA delivery vehicles.

L9 ANSWER 10 OF 61 CAPLUS COPYRIGHT 2006 ACS on STN  
AN 2005:1006376 CAPLUS <<LOGINID:20060811>>  
TI RNAi suppresses polyglutamine-induced neurodegeneration in a model of spinocerebellar ataxia  
AU Xia, Haibin; Mao, Qinwen; Eliason, Steven L.; Harper, Scott Q.; Martins, Ines H.; Orr, Harry T.; Paulson, Henry L.; Yang, Linda; Kotin, Robert M.; Davidson, Beverly L.  
CS Program in Gene Therapy and Dep. of Internal Med., Univ. of Iowa, Iowa City, IA, USA  
SO Nature Medicine (New York, NY, United States) (2005), 11(9, Suppl.), 9-13  
CODEN: NAMEFI; ISSN: 1078-8956  
PB Nature Publishing Group  
DT Journal  
LA English  
AB The dominant polyglutamine expansion diseases, which include spinocerebellar ataxia type 1 (SCA1) and Huntington disease, are progressive, untreatable, neurodegenerative disorders. In inducible mouse models of SCA1 and Huntington disease, repression of mutant allele

expression improves disease phenotypes. Thus, therapies designed to inhibit expression of the mutant gene would be beneficial. Here we evaluate the ability of RNA interference (RNAi) to inhibit polyglutamine-induced neurodegeneration caused by mutant ataxin-1 in a mouse model of SCA1. Upon intracerebellar injection, recombinant adeno-assocd. virus ( \*\*\*AAV\*\*\* ) vectors expressing short \*\*\*hairpin\*\*\* RNAs profoundly improved motor coordination, restored cerebellar morphol. and resolved characteristic ataxin-1 inclusions in Purkinje cells of SCA1 mice. Our data demonstrate in vivo the potential use of RNAi as therapy for dominant neurodegenerative disease.

L9 ANSWER 11 OF 61 CAPLUS COPYRIGHT 2006 ACS ON STN  
AN 2004:606556 CAPLUS <<LOGINID::20060811>>  
DN 141:135179  
TI Recombinant adeno-associated virus expressing RNAi for RNA interference in gene therapy of cardiovascular diseases and cancers  
IN Wu, Xiaobing; Dong, Xiaoyan; Ma, Xin; Lu, Xiaochun; Hou, Yunde  
PA AGTC Gene Technology Company Ltd., Peop. Rep. China  
SO PCT Int. Appl., 53 pp.  
CODEN: PIXXD2  
DT Patent  
LA Chinese  
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004063380	A1	20040729	WO 2003-CN939	20031107
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	BW, GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZM, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
CN 1498964	A	20040526	CN 2002-149319	20021107
AU 2003284795	A1	20040810	AU 2003-284795	20031107
PRAI CN 2002-149319	A	20021107		
WO 2003-CN939	W	20031107		

AB The invention relates to a series of recombinant adeno-assocd. virus that mediates RNA interference (RNAi) for gene therapy of cardiovascular diseases and cancers. The recombinant \*\*\*AAV\*\*\* vectors contain a promoter from U6 snRNA or H1RNA gene to control siRNA expression specific to therapeutic target genes. The targeted genes include those for phospholamban, angiotensin receptor 1, VEGF, cyclin D1, telomerase RNA, and TNF.alpha., for the treatment of heart diseases, cancer, and hypertension. The feasibility of the method is demonstrated using pSNAV/U6/Luc expressing short \*\*\*hairpin\*\*\* -loop interference RNA specific to luciferase gene. The RNAi with a short \*\*\*hairpin\*\*\* -loop of luciferase gene is shown to have 50% and 70% inhibitory activity of luciferase in pMAMneoLuc co-transfected BHK-21 cells and luciferase stable cell lines resp.

L9 ANSWER 12 OF 61 CAPLUS COPYRIGHT 2006 ACS ON STN  
AN 2004:484033 CAPLUS <<LOGINID::20060811>>  
DN 141:135024  
TI Cloning and characterization of a bovine adeno-associated virus  
AU Schmidt, Michael; Katano, Hisako; Bossis, Ioannis; Chiorini, John A.  
CS Gene Therapy and Therapeutics Branch, National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, MD, 20892, USA  
SO Journal of Virology (2004), 78(12), 6509-6516  
CODEN: JOVIAM; ISSN: 0022-538X  
PB American Society for Microbiology  
DT Journal  
LA English

AB To better understand the relationship between primate adeno-assocd. viruses (AAVs) and those of other mammals, the authors have cloned and sequenced the genome of an \*\*\*AAV\*\*\* found as a contaminant in two isolates of bovine adenovirus that was reported to be serol. distinct from primate AAVs. The bovine \*\*\*AAV\*\*\* (BAAV) genome has 4693 bp, and its organization is similar to that of other \*\*\*AAV\*\*\* isolates. The left-hand open reading frame (ORF) and both inverted terminal repeats (ITRs) have the highest homol. with the rep ORF and ITRs of \*\*\*AAV\*\*\* serotype 5 ( \*\*\*AAV\*\*\* -5) (89 and 96%, resp.). However, the right-hand ORF was only 55% identical to the \*\*\*AAV\*\*\* -5 capsid ORF; it had the highest homol. with the capsid ORF of \*\*\*AAV\*\*\* -4 (76%). By comparing the BAAV cap sequence with a model of an \*\*\*AAV\*\*\* -4 capsid, the authors mapped the regions of BAAV VP1 that are divergent from \*\*\*AAV\*\*\* -4. These regions are located on the outside of the capsid and are partially located in exposed loops. BAAV was not neutralized by antisera raised against recombinant \*\*\*AAV\*\*\* -2, \*\*\*AAV\*\*\* -4, or \*\*\*AAV\*\*\* -5, and it demonstrated a unique cell tropism profile in four human cancer cell lines, suggesting that BAAV might have transduction activity distinct from that of other isolates. A murine model of salivary gland gene transfer was used to evaluate the in vivo performance of recombinant BAAV. Recombinant BAAV-mediated gene transfer was 11 times more efficient than that with \*\*\*AAV\*\*\* -2. Overall, these data suggest that vectors based on BAAV could be useful for gene transfer applications.

RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD

#### ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 13 OF 61 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN  
DUPLICATE 7  
AN 2004346733 EMBASE <<LOGINID::20060811>>  
TI RNAi suppresses polyglutamine-induced neurodegeneration in a model of spinocerebellar ataxia.  
AU Xia H.; Mao Q.; Eliason S.L.; Harper S.Q.; Martins I.H.; Orr H.T.; Paulson H.L.; Yang L.; Kotin R.M.; Davidson B.L.

CS B.L. Davidson, Program in Gene Therapy, University of Iowa, Iowa City, IA, United States. beverly-davidson@uiowa.edu  
SO Nature Medicine, (2004) Vol. 10, No. 8, pp. 816-820. .  
Refs: 25  
ISSN: 1078-8956 CODEN: NAMEFI  
CY United Kingdom  
DT Journal; Article  
FS 008 Neurology and Neurosurgery  
LA English  
SL English  
ED Entered STN: 9 Sep 2004  
Last Updated on STN: 9 Sep 2004

AB The dominant polyglutamine expansion diseases, which include spinocerebellar ataxia type 1 (SCA1) and Huntington disease, are progressive, untreatable, neurodegenerative disorders. In inducible mouse models of SCA1 and Huntington disease, repression of mutant allele expression improves disease phenotypes. Thus, therapies designed to inhibit expression of the mutant gene would be beneficial. Here we evaluate the ability of RNA interference (RNAi) to inhibit polyglutamine-induced neurodegeneration caused by mutant ataxin-1 in a mouse model of SCA1. Upon intracerebellar injection, recombinant adeno-associated virus ( \*\*\*AAV\*\*\* ) vectors expressing short \*\*\*hairpin\*\*\* RNAs profoundly improved motor coordination, restored cerebellar morphology and resolved characteristic ataxin-1 inclusions in Purkinje cells of SCA1 mice. Our data demonstrate in vivo the potential use of RNAi as therapy for dominant neurodegenerative disease.

L9 ANSWER 14 OF 61 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN  
DUPLICATE 8  
AN 2004084636 EMBASE <<LOGINID::20060811>>  
TI The Nuclease Domain of Adeno-Associated Virus Rep Coordinates Replication Initiation Using Two Distinct DNA Recognition Interfaces.  
AU Hickman A.B.; Ronning D.R.; Perez Z.N.; Kotin R.M.; Dyda F.  
CS F. Dyda, Laboratory of Molecular Biology, Natl. Inst. Diabet. Digest. K., National Institutes of Health, Bethesda, MD 20892, United States. dyda@ultra.niddk.nih.gov  
SO Molecular Cell, (13 Feb 2004) Vol. 13, No. 3, pp. 403-414. .  
Refs: 58  
ISSN: 1097-2765 CODEN: MOCEFL  
CY United States  
DT Journal; Article  
FS 004 Microbiology  
LA English  
SL English  
ED Entered STN: 18 Mar 2004  
Last Updated on STN: 18 Mar 2004

AB Integration into a particular location in human chromosomes is a unique property of the adeno-associated virus ( \*\*\*AAV\*\*\* ). This reaction requires the viral Rep protein and \*\*\*AAV\*\*\* origin sequences. To understand how Rep recognizes DNA, we have determined the structures of the Rep endonuclease domain separately complexed with two DNA substrates: the Rep binding site within the viral inverted terminal repeat and one of the terminal \*\*\*hairpin\*\*\* arms. At the Rep binding site, five Rep monomers bind five tetranucleotide direct repeats; each repeat is recognized by two Rep monomers from opposing faces of the DNA. Stem-loop binding involves a protein interface on the opposite side of the molecule from the active site where ssDNA is cleaved. Rep therefore has three distinct binding sites within its endonuclease domain for its different DNA substrates. Use of these different interfaces generates the structural asymmetry necessary to regulate later events in viral replication and integration.

L9 ANSWER 15 OF 61 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN  
DUPLICATE 9  
AN 2004466978 EMBASE <<LOGINID::20060811>>  
TI Inhibition of human immunodeficiency virus type 1 replication by siRNA targeted to the highly conserved primer binding site.  
AU Han W.; Wind-Rotolo M.; Kirkman R.L.; Morrow C.D.  
CS caseym@uab.edu  
SO Virology, (5 Dec 2004) Vol. 330, No. 1, pp. 221-232. .  
Refs: 60  
ISSN: 0042-6822 CODEN: VIRLAX  
PUI S 0042-6822(04)00628-2  
CY United States  
DT Journal; Article  
FS 004 Microbiology  
LA English  
SL English  
ED Entered STN: 29 Nov 2004  
Last Updated on STN: 29 Nov 2004

AB The initiation of HIV-1 reverse transcription occurs at an 18-nucleotide sequence in the viral genome designated as the primer binding site (PBS), which is complementary to the 3' terminal nucleotides of tRNA(Lys,3). Since the PBS is highly conserved among all infectious HIV-1, it

represents an attractive target for the development of new therapeutics to inhibit viral replication. In this study, we have evaluated three approaches using small interfering RNA (siRNAs) targeted to the PBS for the capacity to inhibit HIV-1 replication. In the first, transfection of a 21-nucleotide siRNA complementary to the PBS into cells inhibited production of HIV-1 following infection. Control siRNAs of the same length complementary to HIV-1 gag mRNA or to gfp mRNA decreased the production of virus or had no effect on virus replication, respectively. Analysis of the PBS of integrated proviruses derived from viruses that ultimately grew in cultures transfected with siRNA all contained wild-type PBS sequence, demonstrating that HIV-1 did not mutate to escape inhibition by siRNA. In the second approach, \*\*\*hairpin\*\*\* siRNA targeted to the wild-type PBS were expressed using an adeno-associated virus ( \*\*\*AAV\*\*\* ) vector. HIV-1 replication was inhibited in cells infected with \*\*\*AAV\*\*\* encoding the siRNA to the wild-type PBS, but not in cells infected with \*\*\*AAV\*\*\* encoding an siRNA of the same length targeted to an irrelevant PBS. Finally, studies from this laboratory have shown that alteration of the PBS to be complementary to tRNA(His) results in the production of infectious virus that rapidly reverts to utilize tRNA (Lys,3) following in vitro culture. A proviral genome containing a PBS complementary to tRNA(His) that encodes an siRNA molecule complementary

to

the wild-type PBS under control of a U6 promoter within the nef gene was as infectious as the parent HIV-1 genome containing no insert in nef. The virus with the PBS only complementary to tRNA(His) reverted to use tRNA (Lys,3), coincident with rapid virus growth, while the virus encoding siRNA grew slower than the virus without siRNA and maintained the PBS complementary to tRNA(His) longer in culture. At later times of infection, viruses with the PBS complementary to tRNA(His) and the siRNA exhibited a rapid increase in p24 antigen in the culture. Analysis of the PBS revealed that it was now complementary to tRNA(Lys,3). Analysis of the gene encoding the siRNA revealed that the reversion of the PBS coincided with the deletion of the gene encoding siRNA. The results of these studies show that siRNA targeted to the PBS of HIV-1 can inhibit virus replication, supporting the concept that HIV-1 has evolved a strong preference to select tRNA(Lys,3) for high-level replication and establishing the PBS and primer selection as a potential target for new therapeutics. .COPYRIGHT. 2004 Elsevier Inc. All rights reserved.

L9 ANSWER 16 OF 61 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 10

AN 2003371063 EMBASE <<LOGINID::20060811>>

TI Use of adeno-associated viral vector for delivery of small interfering RNA.

AU Tomar R.S.; Matta H.; Chaudhary P.M.

CS P.M. Chaudhary, Hamon Ctr. Therapeut. Oncol. Res., Univ. of TX Southwestern Med. Center, 5323 Harry Hines Blvd., Dallas, TX 75390-8593, United States. preet.chaudhary@utsouthwestern.edu

SO Oncogene, (28 Aug 2003) Vol. 22, No. 36, pp. 5712-5715. .

Refs: 17

ISSN: 0950-9232 CODEN: ONCNE5

CY United Kingdom

DT Journal; Article

FS 004 Microbiology

016 Cancer

022 Human Genetics

037 Drug Literature Index

039 Pharmacy

LA English

SL English

ED Entered STN: 25 Sep 2003

Last Updated on STN: 25 Sep 2003

AB Post-transcriptional gene silencing by small interfering RNAs (siRNAs) is rapidly becoming a powerful tool for genetic analysis of mammalian cells. Delivery of siRNA into mammalian cells is usually achieved via the transfection of double-stranded oligonucleotides or plasmids encoding RNA polymerase III promoter-driven small \*\*\*hairpin\*\*\* RNA. Recently, retroviral vectors have been used for siRNA delivery, which overcome the problem of poor transfection efficiency seen with the plasmid-based systems. However, retroviral vectors have several limitations, such as the need for active cell division for gene transduction, oncogenic potential, low titers and gene silencing. In this report, we have adapted a commercially available adenoassociated virus ( \*\*\*AAV\*\*\* ) vector for siRNA delivery into mammalian cells. We demonstrate the ability of this modified vector to deliver efficiently siRNA into HeLa S3 cells and downregulate p53 and caspase 8 expression. Our results suggest that \*\*\*AAV\*\*\* -based vectors are efficient vectors for the delivery of siRNA into mammalian cells. Based on the known ability of these vectors to infect both dividing and nondividing cells, their use as a therapeutic tool for the delivery of siRNA deserves further study.

L9 ANSWER 17 OF 61 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

AN 2004:151161 BIOSIS <<LOGINID::20060811>>

DN PREV200400147405

TI Inhibition of PU.1 expression by RNA interference.

AU Sun, Amanda [Reprint Author]; Boden, Daniel; Ramratnam, Bharat; Quesenberry, Peter; Rosmarin, Alan [Reprint Author]

CS Hematology/Oncology, Brown University, Providence, RI, USA

SO Blood, (November 16 2003) Vol. 102, No. 11, pp. 567a. print. Meeting Info.: 45th Annual Meeting of the American Society of Hematology. San Diego, CA, USA. December 06-09, 2003. American Society of Hematology.

CODEN: BLOOAW. ISSN: 0006-4971.

DT Conference; (Meeting)

Conference; (Meeting Poster)

Conference; Abstract; (Meeting Abstract)

LA English

ED Entered STN: 17 Mar 2004

Last Updated on STN: 17 Mar 2004

AB Introduction of double stranded (ds) RNA into a cell leads to sequence specific hybridization and degradation of homologous RNA species. This phenomenon, termed RNA interference (RNAi), has emerged as a powerful tool to probe the function of genes in vitro. Compared to antisense mediated gene inhibition, RNAi has the advantage of offering greater sensitivity and specificity, and provides a reliable and reproducible means for gene silencing. RNAi can be achieved in mammalian cells by the cellular introduction of short interfering (si) RNA. Recently, RNAi has been applied to several models of malignant disease and holds the promise of becoming a therapeutic modality in oncology. All mature cellular elements of blood are derived from hematopoietic stem cells (HSCs) and gene transcription is a key regulatory mechanism in hematopoietic differentiation. PU.1 is a transcription factor that controls the transcription of many critical genes in myeloid cells (granulocytes and monocytes). Genetic disruption of PU.1 in mice abrogated fetal myelopoiesis. However because PU.1 disruption caused perinatal lethality, its role could not be defined in adult hematopoiesis. Silencing of PU.1 expression will be used as proof of principle that by RNAi we can successfully block gene expression in hematopoietic cells. The on going research presented here is focused on developing techniques to apply RNAi to HSCs and to down-regulate PU.1 in hematopoietic differentiation. To engineer cellular expression of siRNA, a vector (pSILENCER) containing an expression cassette was constructed that allowed the intracellular synthesis of different siRNA. The expression cassette consists of an upstream MTD (modified-IRNA-derived) pol III-type promoter followed by the suboned target sequence. For long term, stable genetic transfer of specific siRNAs, the entire expression cassette was introduced into an adeno-associated virus-2 ( \*\*\*AAV\*\*\* -2) transduction system. Four distinct 19 nt siRNA molecules were designed based on the nucleotide sequence of murine PU.1 mRNA. The criteria for siRNA design were: (1) 60-80 base pairs downstream of the start codon, (2) GC content around 50%, (3) two AA nucleotides at the 5' end of the siRNA target sequence. The sequences were subsequently engineered as a direct repeat with 6bp spacer and a Xba I and Xho I site for subcloning. Complementary PU.1 DNA oligos corresponding to sense and antisense sequences were inserted into the expression cassette. The predicted transcripts from such direct repeats are small \*\*\*hairpin\*\*\* RNAs (shRNA) which can be processed to siRNAs and mediate silencing (Brummelkamp, Science 2002). The PU.1 pAAV-SILENCER

constructs were introduced into an eukaryotic cell line(293T) in a transient transfection system and the specificity and effectiveness of PU.1 shRNAi were determined by Western blot and real time PCR. Similar approaches will be utilized to silence PU.1 expression in murine hematopoietic cell lines and in primary bone marrow cells and the consequences on myeloid gene expression, cellular proliferation, and differentiation will be defined. Silencing of PU.1 expression in HSCs is expected to block myeloid differentiation and gene expression during adult hematopoiesis. These approaches of silencing PU.1 will provide methods to manipulate gene expression in normal hematopoiesis and will be powerful new therapeutic tools for leukemia.

L9 ANSWER 18 OF 61 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 11

AN 2003290909 EMBASE <<LOGINID::20060811>>

TI Shuttle PCR-based cloning of the infectious adeno-associated virus type 5 genome.

AU Lee K.; Kim Y.-G.; Jo E.-C.

CS E.-C. Jo, MOGAM Biotech. Research Institute, 341 Pojung-Ri Koosong-Eup, Yongin, Kyonggi-Do 449-913, Korea, Republic of. ejo@mogam.re.kr

SO Journal of Virological Methods, (1 Aug 2003) Vol. 111, No. 2, pp. 75-84. .

Refs: 35

ISSN: 0166-0934 CODEN: JMVMDH

CY Netherlands

DT Journal; Article

FS 004 Microbiology

027 Biophysics, Bioengineering and Medical Instrumentation

LA English

SL English

ED Entered STN: 10 Aug 2003

Last Updated on STN: 10 Aug 2003

AB Adeno-associated virus type 5 (AAV5), which is distinct from the other serotypes of \*\*\*AAV\*\*\*, has attracted considerable interest as a premier gene delivery vector. As do the other serotypes, AAV5 contains its 4.7 kb-sized, single-stranded genome flanked with inverted terminal repeats (ITRs) in a \*\*\*hairpin\*\*\* conformation, which serves frequently as pause and arrest sites for DNA polymerases during PCR. To amplify the full-length of the AAV5 genome in single step, we established a shuttled, long and accurate PCR (LA-PCR) procedure in the present study. Furthermore, helper oligonucleotides, which hybridize with the palindromic sequence elements in ITR, were designed and employed in PCR to prevent the formation of \*\*\*hairpin\*\*\* structures by highly GC-rich ITRs. Consequently, a 4.7 kb-sized PCR product was amplified successfully, and cloned into a pBluescript.RTM. II KS(+) plasmid. Six plasmids, harboring the full-length AAV5 genome, rescued wild type AAV5 viruses on transfection to HeLa and HEK 293 cells, which were co-infected with helper adenoviruses. Western and Southern blot analyses supported further the



fact that the pAAV5 plasmids harbored the full-length AAV5 genome. The PCR method described in this study is applicable for the cloning of genomes containing variable palindromic structures, in addition to \*\*\*AAV\*\*\* genomes of other serotypes.

L9 ANSWER 19 OF 61 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN  
AN 2004:204020 BIOSIS <<LOGINID::20060811>>  
DN PREV200400204563  
TI SiRNA mediated inhibition of hippocampal calcium calmodulin kinase II.  
AU Babcock, M. [Reprint Author]; Poulsen, D. J.; Allen, S. [Reprint Author]; Knisely, A.; Paden, C. M.  
CS Psychology, Montana State Univ, Univ. of Montana, Missoula, MT, USA  
SO Society for Neuroscience Abstract Viewer and Itinerary Planner, (2003) Vol. 2003, pp. Abstract No. 736.12. <http://sfn.scholarone.com>. e-file.  
Meeting Info.: 33rd Annual Meeting of the Society of Neuroscience. New Orleans, LA, USA. November 08-12, 2003. Society of Neuroscience.  
DT Conference; (Meeting)  
Conference; Abstract; (Meeting Abstract)  
LA English  
ED Entered STN: 14 Apr 2004  
Last Updated on STN: 14 Apr 2004  
AB Hippocampal calcium calmodulin kinase II (CaM kinase) alpha subunit has been implicated in delayed cell death following transient cerebral ischemia and in models of neuronal plasticity. The contribution of the CaM kinase II alpha subunit in these events has been explored using pharmacological blockade and genetic manipulation, however both techniques have limitations. In the present study, we investigated the use of recombinant adeno-associated virus (rAAV) vectors to deliver CaM kinase II-specific siRNA \*\*\*hairpin\*\*\* sequences to the rat hippocampus. Four siRNA \*\*\*hairpin\*\*\* sequences were designed to contain a sense strand of 19 nucleotides targeting different regions within CaM kinase II alpha mRNA. Recombinant \*\*\*AAV\*\*\* vectors were designed to carrying GFP as a marker gene with specific siRNA sequences driven by the U6 promoter. Transfection of cultured C17.2 neural stem cells with the recombinant \*\*\*AAV\*\*\* plasmids results in a significant reduction of CaM kinase alpha subunit expression. The use of adeno-associated virus delivery of siRNA has utility for studying the role of CaM kinase in plasticity and neurodegenerative processes.

L9 ANSWER 20 OF 61 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN  
AN 2004:197560 BIOSIS <<LOGINID::20060811>>  
DN PREV200400198119  
TI Local gene knockdown in the brain using viral - mediated RNA interference (RNAi) .  
AU Hommel, J. D. [Reprint Author]; Sears, R. M. [Reprint Author]; Simmons, D. L. [Reprint Author]; DiLeone, R. J. [Reprint Author]  
CS Psychiatry, UT Southwestern Med. Ctr. Dallas, Dallas, TX, USA  
SO Society for Neuroscience Abstract Viewer and Itinerary Planner, (2003) Vol. 2003, pp. Abstract No. 325.14. <http://sfn.scholarone.com>. e-file.  
Meeting Info.: 33rd Annual Meeting of the Society of Neuroscience. New Orleans, LA, USA. November 08-12, 2003. Society of Neuroscience.  
DT Conference; (Meeting)  
Conference; Abstract; (Meeting Abstract)  
LA English  
ED Entered STN: 14 Apr 2004  
Last Updated on STN: 14 Apr 2004  
AB Conditional mutagenesis is a powerful approach to understanding the cellular and molecular basis of brain function. However, current transgenic methods require long breeding schemes and often lack regional specificity. As an alternative approach, we have developed a viral-mediated system to create local genetic knockdowns based on RNAi technology. We have engineered type 2 adeno-associated virus ( \*\*\*AAV\*\*\* ) to express a short- \*\*\*hairpin\*\*\* RNA and a GFP marker, both from independent transcription units. Two viruses were made, one designed to specifically target the tyrosine hydroxylase gene ( \*\*\*AAV\*\*\* -shTH) and a second negative control designed to express a scramble \*\*\*hairpin\*\*\* sequence. Stereotaxic delivery of the \*\*\*AAV\*\*\* -shTH virus into the brain of adult mice resulted in reduced expression of tyrosine hydroxylase (TH), a dopamine biosynthetic enzyme in midbrain neurons. Two weeks after viral injections, immunohistochemical analysis revealed no detectable TH in most of the infected dopaminergic neurons whereas neurons infected with control virus showed normal expression. In addition, mice with bilateral TH gene knockdowns in the substantia nigra show performance deficits on the rotarod test when compared to control injected mice. We are applying this approach to studies of brain reward circuitry and feeding behavior. This technique provides a rapid and efficient strategy for inhibiting gene expression in specific regions of the adult mouse brain and should find broad applicability in neuroscience and the generation of animal disease models.

=> d his  
(FILE 'HOME' ENTERED AT 15:31:24 ON 11 AUG 2006)  
FILE 'EMBASE, BIOSIS, CAPLUS' ENTERED AT 15:31:41 ON 11 AUG 2006  
FILE 'EMBASE, BIOSIS, CAPLUS' ENTERED AT 15:31:55 ON 11 AUG 2006  
L1 178 S AAV (3A) (ITR OR INVERT? TERMINAL REPEAT)

L2 23 S L1 AND HAIRPIN  
L3 11 DUP REM L2 (12 DUPLICATES REMOVED)  
L4 0 S KISSING EAR  
L5 0 S KISS? EAR  
L6 6199 S AAV  
L7 154 S L6 AND HAIRPIN  
L8 131 S L7 NOT L2  
L9 61 DUP REM L8 (70 DUPLICATES REMOVED)  
=> s l6 and apoptosis  
L10 194 L6 AND APOPTOSIS  
=> s l10 and (tumor or cancer)  
L11 81 L10 AND (TUMOR OR CANCER)  
=> dup rem l11  
PROCESSING COMPLETED FOR L11  
L12 50 DUP REM L11 (31 DUPLICATES REMOVED)  
=> d bib abs  
L12 ANSWER 1 OF 50 CAPLUS COPYRIGHT 2006 ACS on STN  
AN 2006:608462 CAPLUS <<LOGINID::20060811>>  
DN 145:77684  
TI Viral vectors with enhanced transduction properties comprising a chimeric adeno-associated virus ( \*\*\*AAV\*\*\* ) capsid, and therapeutic uses  
IN Bowles, Dawn E.; Li, Chengwen; Rabinowitz, Joseph E.; Grieger, Josh; Agbandje-McKenna, Mavis; Samulski, Richard Jude  
PA University of North Carolina at Chapel Hill, USA; University of Florida Research Foundation, Inc.  
SO PCT Int. Appl., 81 pp.  
CODEN: PIXXD2  
DT Patent  
LA English  
FAN,CNT 1  
PATENT NO. KIND DATE APPLICATION NO. DATE  
PI WO 2006066066 A2 20060622 WO 2005-US45552 20051215  
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW  
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM  
PRAI US 2004-636126P P 20041215  
AB The present invention is based, in part, on the discovery that parvovirus (e.g., an adeno-assocd. virus ( \*\*\*AAV\*\*\* )) capsids can be engineered to incorporate small, selective regions from other parvoviruses that confer desirable properties. The inventors have discovered that in some cases as little as a single amino acid insertion or substitution from a first parvovirus into the capsid structure of another parvovirus to create a chimeric parvovirus is sufficient to confer one or more of the desirable properties of the first parvovirus to the resulting chimeric parvovirus and/or to confer a property that is not exhibited by the first parvovirus or is present to a lesser extent. Demonstrated is the recombinant prodn. of chimeric AAV1, AAV2 and AAV3b viruses. Also demonstrated is improved transduction of skeletal muscle, brain and liver cells.  
=> d his  
(FILE 'HOME' ENTERED AT 15:31:24 ON 11 AUG 2006)  
FILE 'EMBASE, BIOSIS, CAPLUS' ENTERED AT 15:31:41 ON 11 AUG 2006  
FILE 'EMBASE, BIOSIS, CAPLUS' ENTERED AT 15:31:55 ON 11 AUG 2006  
L1 178 S AAV (3A) (ITR OR INVERT? TERMINAL REPEAT)  
L2 23 S L1 AND HAIRPIN  
L3 11 DUP REM L2 (12 DUPLICATES REMOVED)  
L4 0 S KISSING EAR  
L5 0 S KISS? EAR  
L6 6199 S AAV  
L7 154 S L6 AND HAIRPIN  
L8 131 S L7 NOT L2  
L9 61 DUP REM L8 (70 DUPLICATES REMOVED)  
L10 194 S L6 AND APOPTOSIS  
L11 81 S L10 AND (TUMOR OR CANCER)  
L12 50 DUP REM L11 (31 DUPLICATES REMOVED)  
=> s l12 and hairpin  
L13 4 L12 AND HAIRPIN  
=> d bib abs 1-  
YOU HAVE REQUESTED DATA FROM 4 ANSWERS - CONTINUE? Y(N):y  
L13 ANSWER 1 OF 4 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

AN 2001312224 EMBASE <<LOGINID::20060811>>  
 TI Virus-mediated killing of cells that lack p53 activity [2].  
 AU Raj K.; Ogston P.; Beard P.  
 CS P. Beard, Swiss Inst. Exp. Cancer Res. (ISREC), 155, Ch. des Boveresses,  
 1066 Epalinges, Switzerland. peter.beard@isrec.unil.ch  
 SO Nature, (30 Aug 2001) Vol. 412, No. 6850, pp. 914-917. .  
 Refs: 22  
 ISSN: 0028-0836 CODEN: NATUAS  
 CY United Kingdom  
 DT Journal; Article  
 FS 004 Microbiology  
 016 Cancer  
 022 Human Genetics  
 LA English  
 SL English  
 ED Entered STN: 20 Sep 2001  
 Last Updated on STN: 20 Sep 2001  
 AB A major goal of molecular oncology is to identify means to kill cells  
 lacking p53 function. Most current \*\*\*cancer\*\*\* therapy is based on  
 damaging cellular DNA by irradiation or chemicals. Recent reports support  
 the notion that, in the event of DNA damage, the p53 tumour-suppressor  
 protein is able to prevent cell death by sustaining an arrest of the cell  
 cycle at the G2 phase. We report here that adeno-associated virus (   
 \*\*\*AAV\*\*\* ) selectively induces \*\*\*apoptosis\*\*\* in cells that lack  
 active p53. Cells with intact p53 activity are not killed but undergo  
 arrest in the G2 phase of the cell cycle. This arrest is characterized by  
 an increase in p53 activity and p21 levels and by the targeted destruction  
 of CDC25C. Neither cell killing nor arrest depends upon \*\*\*AAV\*\*\*  
 -encoded proteins. Rather, \*\*\*AAV\*\*\* DNA, which is single-stranded  
 with \*\*\*hairpin\*\*\* structures at both ends, elicits in cells a DNA  
 damage response that, in the absence of active p53, leads to cell death.  
 \*\*\*AAV\*\*\* inhibits tumour growth in mice. Thus viruses can be used to  
 deliver DNA of unusual structure into cells to trigger a DNA damage  
 response without damaging cellular DNA and to selectively eliminate those  
 cells lacking p53 activity.

L13 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN  
 AN 2004:292108 CAPLUS <<LOGINID::20060811>>  
 DN 140:315046  
 TI \*\*\*AAV\*\*\* ITR with a pair of \*\*\*hairpin\*\*\* loop as part of nucleic  
 acid drug comprising biotin PNA-clamp and streptavidin for treating  
 \*\*\*tumor\*\*\*  
 IN Wagner, Thomas E.; Yu, Xianzhang  
 PA Greenville Hospital System, USA  
 SO PCT Int. Appl., 23 pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004029278	A2	20040408	WO 2003-US29990	20030925
WO 2004029278	A3	20040610		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MY, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SI, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2500397	AA	20040408	CA 2003-2500397	20030925
AU 2003278882	A1	20040419	AU 2003-278882	20030925
US 2004137626	A1	20040715	US 2003-669641	20030925
EP 1551859	A2	20050713	EP 2003-770397	20030925
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
PRAI US 2002-413450P	P	20020926		
WO 2003-US29990	W	20030925		

AB The present invention relates to a stabilized nucleic acid that kills  
 \*\*\*tumor\*\*\* cells and methods for producing the same. Specifically, the  
 nucleic acid drug comprises pairs of \*\*\*AAV\*\*\* viral inverted terminal  
 repeat \*\*\*hairpin\*\*\* loops which elicit cell \*\*\*apoptosis\*\*\*. The  
 nucleic acid drug comprises nuclear localization signal peptide assocd.  
 with said nucleic acid drug via a PNA-clamp, wherein said PNA-clamp  
 comprises a biotin mol. that is bound to a streptavidin mol., wherein said  
 streptavidin mol. comprises at least one nuclear localization signal  
 peptide, and wherein said PNA-clamp anneals to a target sequence present  
 in said nucleic acid drug. The invention provides the sequence of  
 adeno-assocd. virus inverted terminal repeat. The present invention also  
 provides methods for making such a stabilized nucleic acid drug as well as  
 methods for targeting the drug to a cell nucleus or genome. Accordingly,  
 the nucleic acid drug of the present invention is useful for inducing  
 \*\*\*apoptosis\*\*\* in cells, esp. those lacking p53, such as \*\*\*cancer\*\*\*  
 cells.

L13 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN  
 AN 2002:343744 CAPLUS <<LOGINID::20060811>>  
 DN 136:303483  
 TI Virus which kills \*\*\*cancer\*\*\* cells employing p53 gene mutation  
 AU Noguchi, Kohji

CS Natl. Inst. Infect. Dis., Japan  
 SO Farumashia (2002), 38(4), 342-343  
 CODEN: FARUAW; ISSN: 0014-8601  
 PB Pharmaceutical Society of Japan  
 DT Journal; General Review  
 LA Japanese  
 AB A review on the possible \*\*\*cancer\*\*\* therapy using viruses which kill  
 cells lacking p53 activity. Adeno-assocd. virus ( \*\*\*AAV\*\*\* )  
 selectively induced \*\*\*apoptosis\*\*\* in cells that lack active p53.  
 Cells with intact p53 activity were not killed but underwent arrest in the  
 G2 phase of the cell cycle. Oligonucleotides of \*\*\*hairpin\*\*\* loop  
 region of the single-stranded DNA of \*\*\*AAV\*\*\* elicited a DNA damage  
 response in normal cells, while they led to death in p53-lacking cells.  
 In addn., \*\*\*AAV\*\*\* inhibited \*\*\*tumor\*\*\* growth in mice.

L13 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN  
 AN 2000:85050 CAPLUS <<LOGINID::20060811>>  
 DN 132:148504  
 TI Substantially complete ribozyme libraries and vectors for their expression  
 and selection for phenotypic effects  
 IN Barber, Jack; Welch, Peter; Li, Xinqiang; Tritz, Richard  
 PA Immusol Inc., USA  
 SO PCT Int. Appl., 163 pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000005415	A1	20000203	WO 1999-US16466	19990720
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2335390	AA	20000203	CA 1999-2335390	19990720
AU 9951173	A1	20000214	AU 1999-51173	19990720
AU 750598	B2	20020725		
EP 1097244	A1	20010509	EP 1999-935766	19990720
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002528049	T2	20020903	JP 2000-561361	19990720
US 2003096399	A1	20030522	US 2002-67956	20020205
US 2004259079	A1	20041223	US 2004-898106	20040722
PRAI US 1998-93828P	P	19980722		
US 1999-357741	A1	19990720		
WO 1999-US16466	W	19990720		
US 2002-67956	B1	20020205		

AB The present invention provides a high complexity substantially complete  
 \*\*\*hairpin\*\*\* ribozyme library having a randomized recognition sequence,  
 packaged in a vector and operably linked to a promoter suitable for high  
 level expression in a wide variety of cells. The invention comprises  
 using the library in a variety of selection protocols for identifying,  
 isolating and characterizing known or unknown target RNAs, to reveal the  
 phenotypic effects of such cleavage, and to identify the gene products  
 that produce those phenotypic effects. In order to minimize the toxicity  
 of the full library, the full library is transduced into the host cells,  
 preferably at an m.o.i. of less than 1, and the ribozyme genes of  
 surviving cells are rescued; the new library of rescued ribozyme genes  
 encodes ribozymes that are not fatal to the host cell. In one embodiment,  
 the ribozyme library comprises a collection of adeno-assocd. virus (   
 \*\*\*AAV\*\*\* ) or retroviral vectors contg. nucleic acids encoding  
 \*\*\*hairpin\*\*\* ribozymes in expression cassettes wherein said collection  
 of vectors contains nucleic acids encoding on av. about 90% or more of all  
 possible \*\*\*hairpin\*\*\* ribozyme binding sequences having 8 or more  
 randomized nucleotides. Preferred \*\*\*AAV\*\*\* libraries comprise a pair  
 of inverted terminal repeats (ITRs) of adeno-assocd. viral genome, a  
 selectable marker (e.g., Neor and Hygrror) may be present, and the  
 ribozyme-encoding nucleic acid can be operably linked to a tRNA promoter  
 (e.g., tRNAVal or tRNA<sup>Ser</sup>) or other promoters such as a PGK promoter.

=> FIL STNGUIDE

COST IN U.S. DOLLARS	SINCE FILE	TOTAL
ENTRY	SESSION	
FULL ESTIMATED COST	166.03	169.00

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) SINCE FILE  
 TOTAL

ENTRY	SESSION
CA SUBSCRIBER PRICE	-10.50 -10.50

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FILE CONTAINS CURRENT INFORMATION.  
 LAST RELOADED: Aug 4, 2006 (20060804/UP).

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=> LOG Y

COST IN U.S. DOLLARS	ENTRY	SINCE FILE SESSION	TOTAL
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TOTAL	ENTRY	SESSION	
CA SUBSCRIBER PRICE		0.00	-10.50

STN INTERNATIONAL LOGOFF AT 15:53:26 ON 11 AUG 2006